REMARKS

Claims 1-4, 6-7, and 9-11 have been examined and are amended herein. Accordingly, claims 1-4, 6, 7, and 9-11 are now pending in the application. Reconsideration of all outstanding objections and rejections and reexamination is requested.

Claims 1, 3, 7, and 9-11 are rejected under 35 U.S.C. §112, first paragraph, as containing new matter.

With regard to claim 1 all references to indices have been removed from the claim. The samples are identified as "coded" samples which conforms with the disclosure, 8:5-10, cited by the examiner.

With regard to claims 7 and 11 the term "first biological tissue sample" has been deleted.

With regard to claim 10, the terms objected to by the examiner have been deleted from the claim.

Claims 1-4, 6-7, and 9-11 are rejected under 35 U.S.C. §112, as being indefinite.

With regard to claim 1 the term "based on" has been deleted.

With regard to claims 1, 4, 7, and 11 the term "utilizing" has been deleted.

With regard to claim 4 clarification has been added.

With regard to claims 4, 6, 7, 9, 10, and 11, the terms "corresponding" and "corresponds" have been deleted.

With regard to claim 4, the phrase "the index data" has been deleted.

With regard to claim 7, the phrase "said first biological sample" has been deleted.

With regard to claims 9 and 10, the limitations objected to have been deleted or clarified.

Paragraph [42] has been amended to better describe the operation of the embodiments. No new matter is introduced because the material was taken from the MultiVIS paper incorporated by reference in paragraph [21] to describe mapping of both volume image data and other types of data, such as object identity data, onto a single x,y,z coordinate space.

Claims 1-5 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Heppelmann et al. in view of Cole et al., Farr et al., and Emmert-Buck et al.

One embodiment of the present invention, as recited for example in claims 1, 4, 7, and 11, includes the steps cutting histologically thin serial sections of a biological sample, constructing a multidimensional morphological matrix of image data based on the serial samples,

unattendedly micro dissecting each of the serial samples into a set of micro dissected section samples, and assigning codes to each of the micro dissected section samples that indicate the location of the micro dissected sections samples in the multidimensional morphological matrix of image data.

Each coded incised section sample is then analyzed to obtain biological data characterizing the coded micro dissected section sample. This biological data is then spatially mapped onto the multidimensional morphological spatial matrix to superimpose the biological data upon volume image data indicated by the code assigned to each coded micro dissected section sample.

Heppelmann discloses two different techniques for three-dimensional reconstruction of extended fine tissue structures: a re-embedding technique and a serial section-ESI technique. It also describes true-to-scale three-dimensional reconstructions.

In the re-embedding technique, the extended fine tissue structure is cut into semi-thin serial sections and the semi-thin sections are examined under oil immersion and photographed. If a semi-thin section is selected for ultra-structural examination then the semi-thin section is re-embedded and converted into a series of ultra-thin sections for viewing the ultra-structural detail of the tissue within that section. Heppelmann, page 164, Re-embedding technique, first and second paragraphs.

Further, in the serial section-ESI technique, a set of serial sections is cut and analyzed utilizing ESI. Heppelmann mentions cutting a complete set of alternate semi- and ultra-thin sections of a tissue block. However, all of these sections are then mounted, in their entirety, in sequence on a mesh transmission grid and imaged using ESI. *Id.*, page 165, first paragraph.

The result of the Heppelmann product is a series of images of the sections, as depicted on the left side of Fig. 4, which can be used to form a 3-D reconstruction depicted on the right side of Fig. 4. The serial sections on the left side of Fig. 4 form the x,y planes of the 3-D structure and the location of the sections in the 3-D structure is indicated by a z coordinate.

The reference Cole teaches the use of histologically cut serial sections to precisely identify specific tumor cells within the prostate gland which are then selected and excised for microarray analysis of expression activity.

In Cole, a 3-D representation of a prostate gland is formed by stacking whole-mount transverse sections cut from the sample. Each serial section may be viewed and is annotated to show the locations where cell populations have been dissected and analyzed. By interactively clicking on these annotations the user can query a database for data related to a selected cell population. In Cole

the selection of the cells to be analyzed occurs prior to the dissection of those cells, and those cells are a specific subset of the cells that make up the entirety of the prostate tissue contained in the series of transverse sections.

The Farr reference merely shows that one can study specific cells for a set of several biological parameters at once and includes graphs depicting the relative concentration of a specific chemical as a function of various concentrations of another chemical.

Emmert-Buck discloses placing a thin transparent film over a tissue section, visualizing the tissue section microscopically, and selectively adhering the cells of interest within the tissue section to the film with a fixed-position, short-duration, focused pulse from an infrared laser. The adhered section is removed from the serial section providing the image data.

This rejection is respectfully traversed for the following reasons.

As set forth above, none of the references disclose the steps recited in claim 1, 4, 7, and 11.

The establishment of a *prima facie* case of obviousness requires that all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03.

As set forth above, none of the references disclose the steps recited in claim 1, 4, 7, and 11.

The claims recite features of unattendedly micro dissecting each serial sample into a set of micro dissected section samples, assigning a code to each micro dissected section sample indicating the location of the coded micro dissected section sample in the multi-dimensional image data, analyzing each coded micro dissected section sample to determine biological data characterizing the micro dissected section sample, and superimposing or linking the biological data of the coded micro dissected section sample upon or to volume image data indicated by the code assigned to the coded micro dissected section sample.

These steps are not taught or suggested in the references.

The examiner states regarding Heppelman that:

> Heppelman et al. describes cutting the second set of sections (for ultrastructural examination) and mounting them on single-slot grids to be further examined (page 164, last paragraph) which represents creating a grid pattern across each serial section to create a set of incised section samples for each serial section of the second set, as stated in claims 1, 7, and 11.

> Heppelman et al. describe the sections were mounted in sequence on mesh grids (page 165, lines 12-14) which is reasonably interpreted to be associating each incised section sample with a unique set of indices as it has grids (x and y coordinates) with each individual sample placed in a known location as stated in claims 1 and 4.

However, in Heppelman there is no teaching or suggestion unattendedly micro dissecting a serial section into a set of micro dissected section samples or of assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix. In Heppelman, incising the serial sections would be contrary to the teaching of the reference since the serial sections are analyzed by a microscope. Incising or micro dissecting the sections would destroy their utility for that purpose.

Further, there is no suggestion of assigning a code to coded micro dissected section samples. In Heppelman there is no analysis of samples for biological activity and hence no data to be mapped to the spatial image. Accordingly, there is no motivation to assign codes to the micro dissected tissue samples.

With regard to Cole the examiner states:

> Cole et al. describe methods for preparing micorarrays from microdissected cells (page 40, col. 1, lines 19-25 and 37-39). Cole et al discuss that the above processes allows for the determination of exact physical relationships between morphological data (one set) on which overlay gene expression data (second set)(page 40, col. 1, lines 14-17 and col. 2, lines 16-24) which represent associating indices from each incised section sample of the second set with indices of the morphological tissue space matrix

However, in the cited sections of Cole et al. there is no discussion or suggestion of micro dissecting a serial section into a set of micro dissected section samples or assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix.

In Cole, it is stated that "8 micrometer serial cut slides are prepared from tissue blocks ... revealing all the normal pathology in the Z direction". Thus, the reference teaches that the specimen can be cut into serial sections. In Fig. 1 various selected sections have been annotated as being of interest. There is no teaching or suggestion of unattendedly micro dissecting the serial section into a set of micro dissected section samples.

With regard to Emmert-Buck the examiner states:

> Emmert-Buck et al. describe a laser applied to specific locations of the film to procure specifically targeted cells that can then be transferred (abstract, lines 5-9) which suggest incising grid patterns of the tissue and selecting only particular sections.

However, in the cited section of Emmert-Buck absolutely no teaching or suggestion of micro dissecting a serial section into a set of micro dissected section samples or assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix.

The technique of "visualizing the tissue microscopically, and selectively adhering the cell of interest to the film" described in that reference do not suggest or teach the claimed feature.

Therefore, the claimed feature of unattendedly micro dissecting a serial section into a set of micro dissected section samples and assigning a code to indicate the location of a coded micro dissected section sample in a multidimensional spatial matrix is not taught or suggested in any cited reference.

Accordingly, none of the references disclose the steps recited in claims 1, 4, 7 and 11 and a *prima facie* case of obviousness has not been established.

Further, the establishment of a *prima facie* case of obviousness requires that the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose. MPEP §2143.01.

The fundamental principal of operation in the re-embedding technique of Heppelmann, the 3-D model of Cole, and the laser capture micro-dissection of Emmert-Buck is that an area of interest is selected from a section being viewed for further analysis.

In contrast, the method recited in claims 1, 4, 7, and 11 works on a fundamentally different principle of operation in that the serial sections are unattendedly micro dissected into serial

sections without any selection by an investigator, and the micro dissected sections are further analyzed. This allows selection for further investigation to occur at anytime subsequent to the micro dissecting because the complete data set is available to be mapped onto the multidimensional image matrix. Thus, the present system lends itself to a survey approach rather than a directed selection approach. As described in [35] of the present application this allows for unattended section incising of a large number of specimens.

In contrast, for example, in Cole if an investigator needed data at a location that had not been previously selected, dissected, and analyzed it would be necessary go back and dissect another cell population for analysis which might not be possible. That is because in Cole the investigator selects areas of interest for analysis. As described at [18] of the present application:

> It should be noted that this study focused on only small groups of specific tissue areas, since the microdissection approach requires a skilled operator and is extremely exacting work. Tissue that isn't used for expression analysis is stained for anatomical reconstruction of the gland architecture, rendering it unusable for further expression analysis. Since this approach is targeted to specific areas of the tissue, it is most useful for specifically targeted studies, and is poorly suited for survey-based exploratory analysis.

In Emmert-Buck the investigator selectively adheres cells of interest to the film.

Further, with regard to Heppelman, the proposed combination would change the principle of operation of the primary reference and render it inoperable. If the serial section of Heppelmann were micro dissected into a grid pattern it could not be used for the next step of ultra-structural analysis since the structure of the serial section would have been destroyed.

Accordingly, a prima facie case of obviousness has not been established.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (925) 944-3320.

Respectfully submitted,

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